Bone Mineral Density Response to Estrogen Replacement in Frail Elderly Women
A Randomized Controlled Trial

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The highest incidence of osteoporotic fractures is in women older than 75 years, who constitute a rapidly expanding segment of the US population. Bone mineral density (BMD), which is a strong risk factor for osteoporosis, continues to decline with age. Indeed, recent prospective studies indicate that bone loss not only continues from middle age into old age but may in fact accelerate in elderly persons. Given the progressive increase in physical frailty that typically occurs in elderly women, an osteoporotic fracture, particularly of the hip, often contributes to the loss of functional independence.

Although estrogen-based hormone replacement therapy (HRT) is an established approach for osteoporosis prevention, little is known about the osteoprotective effects of HRT in frail elderly women.

Objective To determine whether HRT increases bone mineral density (BMD) in frail elderly women.

Design and Setting Randomized, double-blind, placebo-controlled trial conducted in a US university-based research center from September 1995 to August 2000.

Participants Sixty-seven women aged 75 years or older with mild-to-moderate physical frailty were included.

Intervention Participants were randomly assigned to receive conjugated estrogens, 0.625 mg/d, plus trimonthly medroxyprogesterone acetate, 5 mg/d for 13 days (n=45), or matching placebo (n=22), for 9 months.

Main Outcome Measures The primary outcome measure was 9-month change in BMD of the lumbar spine and hip, measured by dual-energy x-ray absorptiometry. Secondary outcomes were changes in markers of bone turnover.

Results Based on intention-to-treat analyses, HRT resulted in significantly larger increases in BMD of the lumbar spine than placebo (mean change, 4.3% vs 0.4%; between-group difference, 3.9%; 95% confidence interval [CI], 3.5%-4.3%) and total hip (mean change, 1.7% vs −0.1%; between-group difference, 1.8%; 95% CI, 1.5%-2.1%). Compared with placebo, HRT resulted in significant decreases in serum bone-specific alkaline phosphatase levels (mean change, −24% vs 6%; between-group difference, −30%; 95% CI, −26% to −33%) and urine N-telopeptide levels (mean change, −48% vs 4%; between-group difference, −52%; 95% CI, −47% to −55%).

Conclusions In physically frail elderly women, 9 months of HRT significantly increased BMD compared with placebo in clinically important skeletal regions. Further studies are needed to determine whether these osteogenic effects of HRT in elderly women are associated with a reduction in osteoporotic fractures.

Context Although hormone replacement therapy (HRT) is an established approach for osteoporosis prevention, little is known about the osteoprotective effects of HRT in frail elderly women.

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domized, double-blind, placebo-controlled trial of the effects of HRT on BMD in women aged 75 years or older with mild-to-moderate physical frailty. We hypothesized that HRT would increase the BMD of the lumbar spine and proximal femur in this population.

**METHODS**

**Subjects**

The study was conducted through the Washington University Older Americans Independence Center (OAIC) from September 1995 to August 2000. Recruitment was directed to elderly women, aged 75 years or older, from the community at large and from congregate living sites. Volunteers provided written informed consent to participate in the study, which was approved by the institutional review board of the Washington University School of Medicine.

The research focus of the Washington University OAIC was on the amelioration of physical frailty in elderly persons. Therefore, eligible volunteers were women who had mild-to-moderate physical frailty, as defined by meeting at least 2 of the following 3 criteria: (1) low peak aerobic power (VO2peak) of 11 to 18 mL/min per kg of body weight, (2) self-reported difficulty or need for assistance with 2 instrumental activities of daily living (ADLs) or 1 basic ADL, and (3) modified physical performance test score of 18 to 22 (score range, 0-36). The screening procedures have been described previously.

Exclusion criteria included use of estrogens within the past year, history of breast cancer or other estrogen-dependent neoplasia, history of cancer within the previous 5 years, recent history (≤5 years) of thromboembolic disease, use of drugs that affect bone metabolism in the previous year, or active serious illness. Women taking thyroid hormone who were not on a stable dose for at least the previous 3 months were excluded. Bone mineral density levels were not exclusionary.

**Figure 1.** Flow of Participants Through Study

- 292 Eligible Patients Screened
- 225 Excluded
  - 84 By Exclusion Criteria
  - 141 By Patient Choice
- 67 Randomized
- 22 Assigned to Receive Placebo
  - 2 Withdrawals
  - 2 Withdraw Consent
- 18 Completed Trial
  - 18 Received Treatment per Protocol
  - 2 Received Modified Treatment
  - 22 Included in Analysis
- 45 Assigned to Receive HRT
  - 11 Withdrawals
    - 2 Breast Discomfort
    - 1 Bloating and Vaginal Bleeding
    - 1 Perceived Decline in Well-Being
    - 1 Death Due to Car Crash
    - 6 Medical, Unrelated to Study
- 27 Completed Trial
  - 27 Received Treatment per Protocol
  - 7 Received Modified Treatment
  - 34 Included in Analysis
- 22 Included in Analysis

HRT indicates hormone replacement therapy.

**Markers of Bone Turnover**

Serum bone-specific alkaline phosphatase (BAP) activity (Metra Biosystems Inc, Mountain View, Calif), a marker of bone formation, and urinary cross-linked C-telopeptide of type I collagen (NTX) (Ostex International, Waltham, Mass). Coefficients of variation for these measures in our laboratory in older women have been reported previously.

**Bone Mineral Content and BMD**

Bone mineral content (BMC) and BMD of the total body, lumbar spine, and proximal femur were measured at 3-month intervals during the study using dual-energy x-ray absorptiometry on a QDR-1000W instrument (Hologic Inc, Waltham, Mass). Coefficients of variation for these measures in our laboratory in older women have been reported previously.
Seattle, Wash), a marker of bone resorption, were measured by enzyme-linked immunosorbent assay. Coefficients of variation for these measurements were 4% to 7%.

**Diet Evaluation**
Participants completed 3-day food records at the beginning and end of the study period under supervision by a registered dietitian. Records were analyzed using Nutritionist IV (First Databank, San Bruno, Calif). Based on the initial dietary assessment women were provided supplemental calcium and cholecalciferol to adjust intake to approximately 1200 mg/d and approximately 800 U/d, respectively.

**Statistical Analyses**
Based on our previous studies of the effects of HRT on BMD of postmenopausal women,19,20 the mean (SD) differences in changes in BMD of the lumbar spine and femoral neck between the placebo and HRT groups were projected to be 3.9% (3.4%) and 1.5% (1.8%), respectively. Thus, for the projected sample sizes, the estimated power to detect significant effects of HRT was 98% for lumbar spine BMD and 83% for total hip BMD.

The primary analyses of BMC and BMD data were carried out in an intention-to-treat fashion. Independent t tests were used to determine whether the percent change in outcomes was significantly different in response to HRT compared with placebo. When follow-up data were not available, the last observation was carried forward, which yields conservative results. Secondary analyses were conducted in those women who adhered to treatment and provided follow-up data. Results are presented as mean (SE) unless otherwise stated. SAS version 6.08 (SAS Institute, Cary, NC) was used for all statistical analyses.

**RESULTS**
Of the 67 women enrolled, 54 underwent follow-up evaluations (Figure 1). Two women in the placebo group dropped out and refused final testing for personal reasons; 11 women in the HRT group also dropped out and did not undergo final testing. Compared with the completers, those who dropped out were older (84 [4] vs 81 [3] years, \( P = .03 \)) and had a lower VO_{2\text{peak}} (13 [3] vs 15 [3] mL/min per kg of body weight, \( P = .04 \)), but there were no significant differences in baseline BMC and BMD values.

Participants who were unable to tolerate the prescribed estrogen due to adverse effects (7 HRT, 2 placebo) had the HRT modified. The dosage was reduced to one 0.625-mg tablet every other day for a period of 1 to 4 weeks. The dosage was then increased to 1 tablet daily. Women who continued to be bothered by adverse effects (2 HRT, 1 placebo) returned to a regimen of 3 to 4 tablets per week for the remainder of the study period.

The percentage of prescribed doses taken by women in the placebo group who completed the study averaged 85% (11%) and 99% (4%) for estrogens and MPA, respectively. Compliance in the HRT group was 86% (13%) for estrogens and 86% (33%) for MPA.

The only significant difference between the groups at baseline was the age at menopause, which was younger in the HRT group (Table 1). Total body BMC and BMD of all regions measured tended to be higher in the HRT group but differences were not statistically significant. Based on BMD values for the femoral neck, 91% of women in the placebo group and 93% in the HRT group were osteopenic or osteoporotic according to the criteria of the World Health Organization.

**Diet**
There were no significant differences between the groups at baseline in calcium, vitamin D, or energy intake. Calcium intake averaged 735 (316) and 671 (231) mg/d in the placebo and HRT groups, respectively; at baseline and 1353 (256) and 1366 (266) mg/d, respec-

![Table 1. Baseline Characteristics of Study Groups](https://jama.jamanetwork.com/content/286/7/817.full)
Estrogen Replacement and Bone Mineral Density

Outcomes, at the end of the study period. Vitamin D intake averaged 151 (162) and 138 (81) U/d at baseline in the placebo and HRT groups, respectively, and 756 (107) and 784 (97) U/d, respectively, at the end of the study period.

BMC and BMD

Bone density measurements are shown in Table 2 and Figure 2 as the percentage change from baseline. Based on the intention-to-treat analyses, increases in total BMC and in BMD of the total body, lumbar spine, total hip, and trochanter were significantly larger in response to HRT than placebo treatment. The statistical results remained the same when absolute changes rather than percentage changes in bone measures were used, as well as when baseline bone measures were included in the models as covariates.

Secondary analyses included women who provided final evaluations and were adherent to treatment. Adherence was defined as taking more than 80% of the prescribed dose over the period of study. There were 29 adherent women in the HRT group, including 27 who received standard treatment and 2 in whom treatment was modified for only 1 to 2 weeks. The increases in BMC and BMD tended to be larger in the subset of women who were adherent to HRT than in all women randomized to HRT (Figure 2). In addition, women adherent to HRT had a significant increase in femoral neck BMD when compared with placebo treatment (2.5% vs −0.1%, respectively; between-group difference, 2.6%; 95% confidence interval [CI], 2.1%-3.1%; P = .04).

Markers of Bone Turnover

Urine samples were obtained from 25 women in the HRT group and 16 women in the placebo group for the assessment of NTX. Serum samples for the measurement of BAP were obtained from 30 women in the HRT group and 19 women in the placebo group. Baseline urinary NTX concentrations were 53.2 (6.3) and 52.6 (3.7) nmol/L of bone collagen equivalents per mmol/L of creatinine and baseline serum BAP concentrations were 19.6 (1.7) and 20.5 (1.2) U/L for the placebo and HRT groups, respectively (P > .05 for all). Compared with placebo, HRT resulted in significant decreases in NTX (−48% vs 4%; between-group difference, −52%; 95% CI, −47% to −55%; P < .001) and BAP (−24% vs 6%; between-group difference, −30%; 95% CI, −26% to −33%; P < .001) (Figure 3). The change in NTX was inversely correlated with the change in total body BMC (r = −0.33; P = .02). In addition, the changes in BAP and NTX over the study period were each inversely correlated with changes in total body, lumbar spine, total hip, and trochanter BMD (correlation coefficients from r = −0.28 to r = −0.46; P < .05 for all).

Comment

Because of the prevalence of low BMD and physical frailty in elderly women, osteoporotic fractures pose a major threat to functional independence. Although HRT is one of the most effective means of reducing risk for osteoporosis, there have been few randomized studies of HRT in elderly women, and none that has focused specifically on women older than 75 years. Our study therefore provided novel information on the skeletal response to the initiation of HRT in physically frail elderly women. Hormone replacement therapy resulted in significant increases in BMD of the lumbar spine and hip regions in these women who were at high risk for falls and frac-
Results from both the intention-to-treat and the adherence paradigms indicated that increases in BMD in response to HRT were significantly larger than the changes that occurred in placebo-treated women. It should be noted that the placebo group had stable BMD levels over the 9-month period of study. It is likely that bone loss in this group was attenuated by the calcium and vitamin D supplementation, as has been observed by others.23,24

The magnitude of increase in lumbar spine BMD (4.3%) after 9 months of HRT in these elderly women was similar to the increases reported in previous randomized studies of HRT in women younger than 75 years (3%-8% after 1 year).2,5-8 Importantly, the increases in total hip BMD (1.7%) and trochanter BMD (2.3%) after 9 months of HRT in the intention-to-treat analyses were similar to or greater than those observed in previous studies of older women.2,7,8 Although a significant increase in femoral neck BMD (2.5%) occurred only in women who were adherent to HRT, this provides evidence that HRT is effective at this region when taken as prescribed. Because hip BMD is a strong predictor of hip fractures,25 our findings of positive effects of HRT on hip BMD have potentially important clinical implications for preserving the independence of frail elderly women.

The increase in lumbar spine BMD in elderly women after 9 months of HRT tended to be larger than the increase (3%-3.6%) that occurred in younger women (45-64 years) in the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial after the first year of the 3-year study.21 Although comparisons of findings across studies must be approached cautiously, both the PEPI trial and others2,3 demonstrated that older age and lower initial BMD were associated with a greater BMD response to HRT. The positive effects of HRT on BMD are presumably due, in part, to filling of the remodeling space consequent to the suppression of bone turnover.20-22 Thus, the robust response of elderly women to HRT is likely related to the high rate of skeletal turnover in elderly women. It was once commonly believed that bone turnover remained elevated for only a few years after menopause28-30 and that bone loss subsequently slowed or ceased in older women.31 However, recent studies have provided evidence that bone turnover remains elevated into old age32 and that bone loss may accelerate rather than slow in elderly persons.1 Indeed, our subjects had high rates of bone turnover, as indicated by elevated serum BAP and urine NTX concentrations that decreased significantly in response to HRT.

The standard replacement dose of conjugated estrogens (0.625 mg/d) was used in the current study. Recently, Recker et al8 reported that a lower dose (0.3 mg/d) coupled with adequate calcium and vitamin D intake increased BMD in women older than 65 years. Using an intention-to-treat approach, they found an increase in spine BMD of about 2% after 12 months of HRT that continued to increase through year 3, peaking at 4%. We observed an increase in spinal BMD of 4.3% after only 9 months of standard HRT. Among women who were at least 90% adherent to HRT in the study by Recker et al, femoral neck BMD increased by 1.6% in 3 years. In the present study, women who were at least 80% adherent to HRT had an increase in femoral neck BMD of 2.5% after 9 months. It will be important to further evaluate the dose-response effects (benefits, risks, and adherence) of HRT in elderly women in a larger controlled trial.

Although there was some early intolerance to HRT, symptoms were substantially decreased by temporary dose reduction in most cases. Furthermore, medical reasons unrelated to HRT were primarily responsible for study discontinuation in our sample. The HRT attrition rate in our study was 24% compared with 8% to 20% in previous trials of HRT in younger postmenopausal women.2,7,8,21

Our study contributes to the growing evidence suggesting the positive effects of HRT on the skeletal health of women in late life. Traditional thought has been that the estrogen-dependent compartment of bone becomes depleted approximately 15 years after menopause. Riggs et al33 have challenged this concept by proposing a “unitary model,” in which estrogen deficiency is also primarily responsible for the decline in bone mass that previously had been attributed to the aging process. Although their hypothesis still must be proven, the effects of estrogens on calcium conservation through extraskeletal organs may be a plausible mechanism for the positive effects of HRT on BMD in elderly women. For example, estrogen treatment has been shown to preserve intestinal responsiveness to vitamin D,39 increase parathyroid hormone (PTH)-independent tubular reabsorption of calcium,39 and decrease PTH secretion during hypocalcemia.39 Other potential mechanisms include the suppressive effects of estrogens on bone-resorbing cytokines37 associated with the chronic inflammation accompanying aging.38

Our trial had some limitations. The sample size was small, the duration of HRT was limited to 9 months, and we used a physiological (ie, BMD) rather than a clinical (ie, fractures) end point. Because we included only women with physical frailty, it is possible that our find-

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themings are relevant only to frail elderly women willing to take HRT and not to the general population of elderly women. Although our study suggests that physically frail women are candidates for the osteogenic benefits of HRT, their shorter life expectancy may limit the period over which the benefits would accrue.

In summary, HRT has significant osteogenic effects in very old, physically frail women. However, fracture risk in very old women is due to multiple factors in addition to low BMD, including sensory and neuromuscular impairments, medications, and environmental hazards. Further research is therefore necessary to elucidate the effectiveness of HRT, alone and in combination with fall-prevention measures, in reducing fracture rates and postponing disability in elderly women.

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References